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Original article

Left atrium volume index and pathological features of left atrial appendage as a predictor of failure in postoperative sinus conversion

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Summary
Background: Previous studies showed that some parameters, including left atrium diameter and left atrium volume index (LAVI), predicted the success of sinus conversion. However, no previous studies have investigated the association of sinus conversion with LAVI and histopathological findings. This study was designed to investigate the relationship among LAVI, pathological assessment, and failure in sinus conversion after surgery for valvular atrial fibrillation (AF).
Methods and results: A total of 78 patients with left atrium enlargement and valvular AF who underwent maze procedure concomitantly with various cardiac surgeries were classified into one of two groups: those who successfully underwent sinus conversion (Group 1; $n = 40$) and those who did not achieve sinus conversion (Group 2; $n = 38$). Histopathological assessment was performed in 9 cases using tissues derived from the left atrial appendage (LAA). The degree of histopathological change was classified into 1 of 4 grades. LAVI was significantly less in Group 1 than in Group 2 ($81 \pm 22\,ml/m^2$ vs. $122 \pm 49\,ml/m^2$, $p < 0.001$).

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Preoperative LAVI predicted 100% failure of sinus conversion after surgery with a cut-off value of 135 ml/m^2. Histopathological analyses clearly showed that the grades for intercellular fibrosis, fatty infiltration, endocardial thickening, and nuclear enlargement/abnormalities were significantly and positively correlated with LAVI ($r = 0.75$, $p < 0.05$; $r = 0.74$, $p < 0.05$; $r = 0.69$, $p < 0.05$; $r = 0.77$, $p < 0.05$, respectively).

Conclusions: LAVI associated with histopathological features of the resected LAA is a predictor of failure in sinus conversion following surgical intervention in patients with valvular AF.

Introduction

Atrial fibrillation (AF) is one of the most frequent complications in patients with mitral valve disease and has been shown to increase the risk of systemic embolization and mortality [1,2]. The maze procedure, initially described by Cox et al. [3,4], involves incisions of both atria and can lead to sinus conversion in patients with AF alone as well as in those patients with AF associated with various organic heart diseases [5].

Several investigators have reported that successful sinus conversion in response to the maze procedures can be predicted by certain variables, including age, cardiothoracic ratio (CTR) on chest X-ray, duration of AF, and amplitude of f-wave in the V1 lead [6,7]. Some reports have suggested that left atrial (LA) diameter predicted sinus conversion after surgery for AF [6—8], while other studies have reported that LA diameter does not predict sinus conversion after cardiac surgery [9,10]. By contrast, more recent studies have reported that LA volume may predict the risk of AF or cardiovascular events [11,12] and that left atrium volume index (LAVI) can predict sinus conversion after the maze procedure [10]. Regardless, no previous study has described a cut-off value for preoperative LAVI in predicting failure of sinus conversion after cardiac surgery for patients with AF and mitral disease. Further, although histopathological changes in resected left atrial appendages (LAA) or LA have also been studied in AF patients [13—15], there have been few reports that investigated the association between histopathology and success of sinus conversion [16].

Thus, the goal of the present study was to determine the specific utility of preoperative LAVI in predicting failure of sinus conversion after surgical treatment for AF in patients with LA enlargement and valvular heart disease.

Materials and methods

Patient population

Seventy-eight patients with LA enlargement and valvular AF, who underwent maze procedure concomitantly with various cardiac surgeries for persistent AF and organic valvular heart disease at Kagoshima University Hospital between January 2000 and January 2006 were enrolled in this study. All patients had mitral valve disease or other organic valvular disease with AF for >4 weeks. The patient population consisted of 37 men and 41 women, with a mean age of 64 ± 9 years (age range, 29—84 years). Patients were classified into one of two groups: those who successfully underwent sinus conversion from AF (Group 1; $n = 40$), and those in whom AF persisted (Group 2; $n = 38$). The success of sinus conversion after surgery for AF was defined as persistence in sinus rhythm without the use of antiarrhythmic drugs or electrical cardioversion after 4 weeks of follow-up.

Surgical procedure

Detailed surgical techniques of Kosakai maze, cryo-maze, and radiofrequency ablation have been reported previously [5,17,18]. Underlying heart disease and concomitant surgical procedures are summarized in Table 1.

Electrocardiography

All of the patients enrolled in this study showed persistent AF. Patients with paroxysmal AF were excluded from this study. A diagnosis of paroxysmal AF was established if AF terminated spontaneously and had generally lasted for less than 48 h on standard 12-lead electrocardiography (ECG) or 24-hour Holter ECG recordings. Cardiac rhythm was continuously monitored for 1 week and follow-up 12-lead ECG was recorded every week for 4 weeks postoperatively. The success of sinus conversion after surgery for AF was defined as persistence in sinus rhythm without the use of antiarrhythmic drugs or electrical cardioversion after 4 weeks of follow-up. The atrial fibrillatory wave with the greatest size was measured in the V1 lead for at least 10 cardiac cycles. It was measured from the upper edge of the peak to the lower edge of trough [6].

Echocardiography

Trans-thoracic echocardiography was performed with a 2.5-MHz transducer attached to a commercially available echo Doppler machine (ATL HDI 3000, Bothell, WA, USA; Toshiba SSH 380A, Tokyo, Japan; Philips Medical Systems Sonos 5500, Andover, MA, USA; Aloka SSD-5500, Tokyo, Japan; Siemens Sequoia 512, Mountain View, CA, USA) before and at 4 weeks postoperatively in all patients. M-mode measurements were performed according to the recommendation of the American Society of Echocardiography. LA volume was measured by planimetry in the four-chamber view and two-chamber view with the area length method (LA volume $= 0.85 \times A1 \times A2/L$; $A1$, area of 4-chamber view; $A2$, area of 2-chamber view; L, LA longitudinal length), and maximum area was measured (at the end of the T wave on the ECG) and averaged over more than five beats by two independent observers [19]. LAVI was calculated as LA volume divided by body surface area. All preoperative echocardiograms and other parameters were reviewed in a blinded fashion.

Table 1 Underlying heart disease and concomitant surgical procedures in the 2 groups.

	Group 1 ($n = 40$)	Group 2 ($n = 38$)	p-Value
Associated heart disease			
Mitral stenosis	11 (28%)	10 (26%)	0.91
Moderate	7 (18%)	6 (16%)	
Severe	4 (10%)	4 (11%)	
Mitral regurgitation	25 (63%)	25 (66%)	0.76
Moderate	13 (33%)	12 (32%)	
Severe	12 (30%)	13 (34%)	
Mitral stenosis + regurgitation	3 (8%)	1 (3%)	0.33
Aortic valve disease	5 (13%)	4 (11%)	0.79
Tricuspid valve disease	19 (48%)	21 (55%)	0.49
Coronary artery disease	4 (10%)	6 (16%)	0.45
Atrial septal defect	3 (8%)	2 (5%)	0.69
Maze procedure			
Cryoablation	19 (48%)	19 (50%)	0.83
Radiofrequency ablation	19 (48%)	21 (55%)	0.49
Concomitant procedures			
Mitral valve replacement	15 (38%)	13 (34%)	0.76
Mitral valve repair	20 (50%)	19 (50%)	1.00
Mitral annuloplasty	4 (10%)	3 (8%)	0.75
Aortic valve replacement	5 (13%)	3 (8%)	0.50
Tricuspid annuloplasty	25 (63%)	21 (55%)	0.52
Coronary artery bypass grafting	4 (10%)	6 (16%)	0.44
Atrial septal defect repair	3 (8%)	2 (5%)	0.69

Values given as % patients.

Medications

Anticoagulation therapy with warfarin and/or aspirin was used in all patients. Cardioversion and/or antiarrhythmic drugs were not employed for the restoration of sinus rhythm after the surgical treatment during the follow-up period in order to observe the success rate of sinus conversion as a result of the surgical treatment.

Histopathological assessment

Nine patients provided informed consent for histopathological assessment of the LAA. After excision of tissue during the operative procedure, LAA tissues were immediately fixed in 20% neutral buffered formalin. The LAA were transversely sectioned serially at intervals of 2-mm. Each 2-mm LAA section was routinely processed and embedded in paraffin. Five serial 5-μm thick slices from each slab were mounted, and 4 slices were stained with either hematoxylin and eosin stain, Masson's trichrome stain, Weigert's elastic van Gieson's stain, and phosphotungstic acid-hematoxylin stain, respectively. The following histopathologic parameters were assessed: (1) intercellular fibrosis (ICF): degree of ICF in the subendocardium, myocardium, and subepicardium; (2) fatty infiltration: degree of fatty infiltration in the myocardium; (3) endocardial thickening: thickness of the endocardium of the LAA; (4) myocardium: degeneration (lytic change) of myocardium; (5) cardiomyocyte: size (hypertrophy and irregular cell size) and vascular degeneration; and (6) nuclei: size (enlargement) and abnormality of shape (bizarre nuclear shape). The degree of histopathological change was graded as follows: none $\sim$ minimum (score 0); mild (score 1); moderate (score 2); severe (score 3) according to Ih and Saitoh [20]. Two independent investigators (who were blinded as to which patients had developed postoperative AF) examined the specimens. Scoring was conducted at a magnification of 10$\times$, 25$\times$, 50$\times$, 100$\times$, and/or 200$\times$ in histological sections. A minimum of 30 microscopic fields of each LAA was examined.

Statistical analysis

Values for continuous variables are expressed as the mean $\pm$ SD. Categorical variables were compared using the Chi-square test or the Fisher exact test (two-tailed). Comparison of continuous variables was performed by the two sample Student's t-test for normally distributed data, and by the Mann—Whitney U-test for non-normally distributed data. All statistically significant variables from the univariate models consisted of conventional predictors and were placed in the multiple variable models, which were retained, no further selection processes were performed. Linear discriminant analysis was performed to determine the cut-off value of significant preoperative variables in predicting the 100% failure (100% specificity), and the small-

Table 2 Clinical characteristics in the 2 groups.

	Group 1 ($n=40$)	Group 2 ($n=38$)	p-Value
Men	23 (58%)	17 (43%)	0.51
Body surface area (m^2)	1.59 ± 0.14	1.54 ± 0.17	0.14
Hypertension	16 (40%)	12 (32%)	0.44
Hyperlipidemia	10 (25%)	14 (37%)	0.26
Diabetes mellitus	5 (13%)	5 (13%)	0.93
Smoker	12 (30%)	12 (32%)	0.80
Renal dysfunction	3 (8%)	5 (13%)	0.42
Systolic blood pressure (mmHg)	119 ± 17	115 ± 14	0.28
Diastolic blood pressure (mmHg)	71 ± 12	66 ± 12	0.07
Mean blood pressure (mmHg)	87 ± 12	82 ± 11	0.08
Echocardiographic data			
LV dimension at diastole (mm)	53 ± 8	51 ± 10	0.28
LV dimension at systole (mm)	36 ± 9	32 ± 9	0.19
Ventricular septum (mm)	11 ± 2	11 ± 2	0.10
LV posterior wall (mm)	11 ± 2	11 ± 2	0.94
LV mass (g)	234 ± 81	229 ± 81	0.79
Medications			
Aspirin	19 (48%)	15 (39%)	0.47
Warfarin	37 (93%)	31 (82%)	0.15
Digitalis	22 (55%)	17 (45%)	0.35
ACE inhibitors	10 (25%)	5 (13%)	0.18
ARB	13 (33%)	13 (34%)	0.95
Loop diuretic	32 (80%)	30 (79%)	0.92
Spironolactone	16 (40%)	16 (42%)	0.83

LV, left ventricular; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers.
Values given as mean $\pm$ SD or % patients, unless otherwise indicated.

est cut-off value of the preoperative variable was applied to predict the whole population with the failure in sinus conversion. A probability value of <0.05 was considered to represent statistical significance.

Results

Patient characteristics and clinical parameters associated with sinus conversion

Clinical characteristics for the study population are summarized in Table 2. Gender distribution, body surface area, systolic blood pressure, diastolic blood pressure, mean blood pressure, other coronary risk factors, and renal dysfunction were similar when comparing the 2 groups. On echocardiography, left ventricular (LV) dimension at diastole and at systole, intraventricular septal thickness, posterior wall thickness, and LV mass were similar when comparing the 2 groups.

Age, CTR, duration of permanent AF, and LAVI were significantly smaller in Group 1 than in Group 2 (Table 3) but there was no difference in the amplitude of f-wave and LA diameter when comparing the 2 groups.

Univariate logistic regression analysis demonstrated that age, CTR, duration of AF, and LAVI were significantly related with the failure of sinus conversion after surgical treatment. However, our multivariable model including age, CTR, duration AF, and LAVI demonstrated that only LAVI was an independent determinant of failure of sinus conversion after surgical treatment (odds ratio, 1.03; 95% confidence interval, 1.00 to 1.05; $p < 0.02$).

Value of preoperative LAVI in predicting failure of sinus conversion

The smallest cut-off value of the preoperative LAVI was applied to predict the whole population with failure with 100% specificity. The cut-off value of preoperative LAVI to predict failure of sinus conversion after surgery for AF was 135 ml/m^2 (Fig. 1).

Correlation between LAVI and LAA histopathology

Nine patients gave informed consent for histopathological assessment of LAA. Sinus conversion was achieved in 4 of these 9 patients but not in the remaining 5 patients. Intracellular fibrosis, lytic change of myocardium, cardiomyocyte degeneration, and nuclear enlargement/abnormalities were more marked in patients in Group 2 than those in Group 1 (Table 4). Although there was no statistical difference in fatty infiltration and endocardial thickening when comparing the two groups, fatty infiltration and endocardial thickening were more likely marked in patients in Group 2 than those in Group 1.

Histopathologic results are illustrated in Fig. 2. Cases with larger LAVI and failure to convert to sinus rhythm

Table 3 Conventional predictors of success for sinus conversion in the 2 groups.

Variables	Group 1 ($n = 40$)	Group 2 ($n = 38$)	p-Value
Age (years)	62 ± 11	67 ± 8	0.02
Cardiothoracic ratio (%)	56 ± 5	60 ± 6	<0.001
Duration of permanent AF (months)	47 ± 83	102 ± 95	0.01
Amplitude of f-wave in V1	0.26 ± 0.31	0.21 ± 0.13	0.31
Left atrial diameter	53 ± 9	55 ± 8	0.17
Left atrial volume index	81 ± 22	122 ± 49	<0.001

AF, atrial fibrillation.
Values given as mean ± SD.

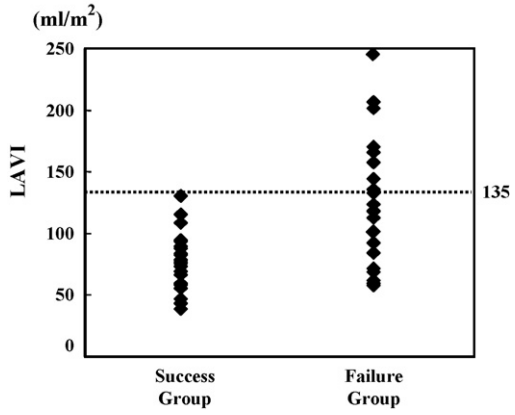

Figure 1 Distribution of left atrial volume index (LAVI) in the 2 groups.

showed marked endocardial thickening and lytic change of myocardium when compared with cases with smaller LAVI who achieved sinus conversion successfully (Fig. 2A, B, E, and F). When lytic change of myocardium was present, the substrate of the atria was also replaced with ICF and fatty tissue (Fig. 2E and F). Furthermore, inspection under high magnification revealed hypertrophy, irregular size, lytic change, vacuolar change in cardiomyocytes, enlargement and abnormalities of nucleus, and the crudeness (the decrease of density and/or uniformity) of myofilaments compared with those of left panels (Fig. 2C, D, G, and H).

According to statistical assessment, intracellular fibrosis, fatty infiltration, endocardial thickening, and nuclear enlargement/abnormalities were significantly and positively correlated with preoperative LAVI, while lytic change of myocardium and degeneration of cardiomyocyte were not (Fig. 3). However, lytic change of myocardium and degeneration of cardiomyocyte were more likely correlated with preoperative LAVI.

Discussion

Previous papers have demonstrated that LA size is a marker of cardiovascular risk factors and an indicator of existing cardiac disease [12,21]. LA diameter alone is known to be an inadequate reflection of LA volume [12,22]. LAVI serves as a predictor of adverse cardiac events and postoperative AF after maze procedure and/or other cardiac surgeries [10—12,22—24]. The present study showed that the preoperative LAVI was a significantly strong predictor of the failure for sinus conversion in patients with valvular AF, despite the fact that LA diameter was not a significant predictor. Our data supports previous findings.

Utility of LAVI

In patients with valvular disease and AF, the myocardium of the atrial free wall is exposed to volume and/or pressure overload. Subsequent dilatation of the left atrium leads to three-dimensional over-extension of atrial wall with extensive intracellular fibrosis and myocardial degeneration. LAVI represents the consequence of chronic pressure overload and volume overload of left atrium. Thus it would supersede the other conventional predictors. Therefore, LAVI has been strongly associated with adverse events [10—12,23,24]. The present study determined the optimal cut-off value (135 ml/m^2) of LAVI as an independent factor to predict the failure of sinus conversion after surgery for valvular AF. Use of this cut-off value may help determine which patients with LA enlargement and persistent AF will benefit from surgical intervention.

Association of LAVI with histopathological changes

AF is associated with structural remodeling and fibrosis [25—27]. Indeed, several histopathological studies of valvular AF have revealed extensive fibrosis in the enlarged atria [14,15], and an increased amount of fibrosis has been seen in the atria of patients with AF when compared with those in sinus rhythm [15,27]. Atrial fibrosis also develops in patients with AF after coronary bypass surgery but not in patients who remain in sinus rhythm [28,29]. This is the first study to demonstrate the relationship between LAVI and histopathological parameters of the LAA, which is consistent with previous observations that histopathological features of LAA may predict persistence/recurrence of AF following surgical intervention [16].

Indeed, various extracellular parameters (intracellular fibrosis, fatty infiltration, endocardial thickening) were significantly associated with LA size, but there was no significant association between myocardial degeneration and LAVI.

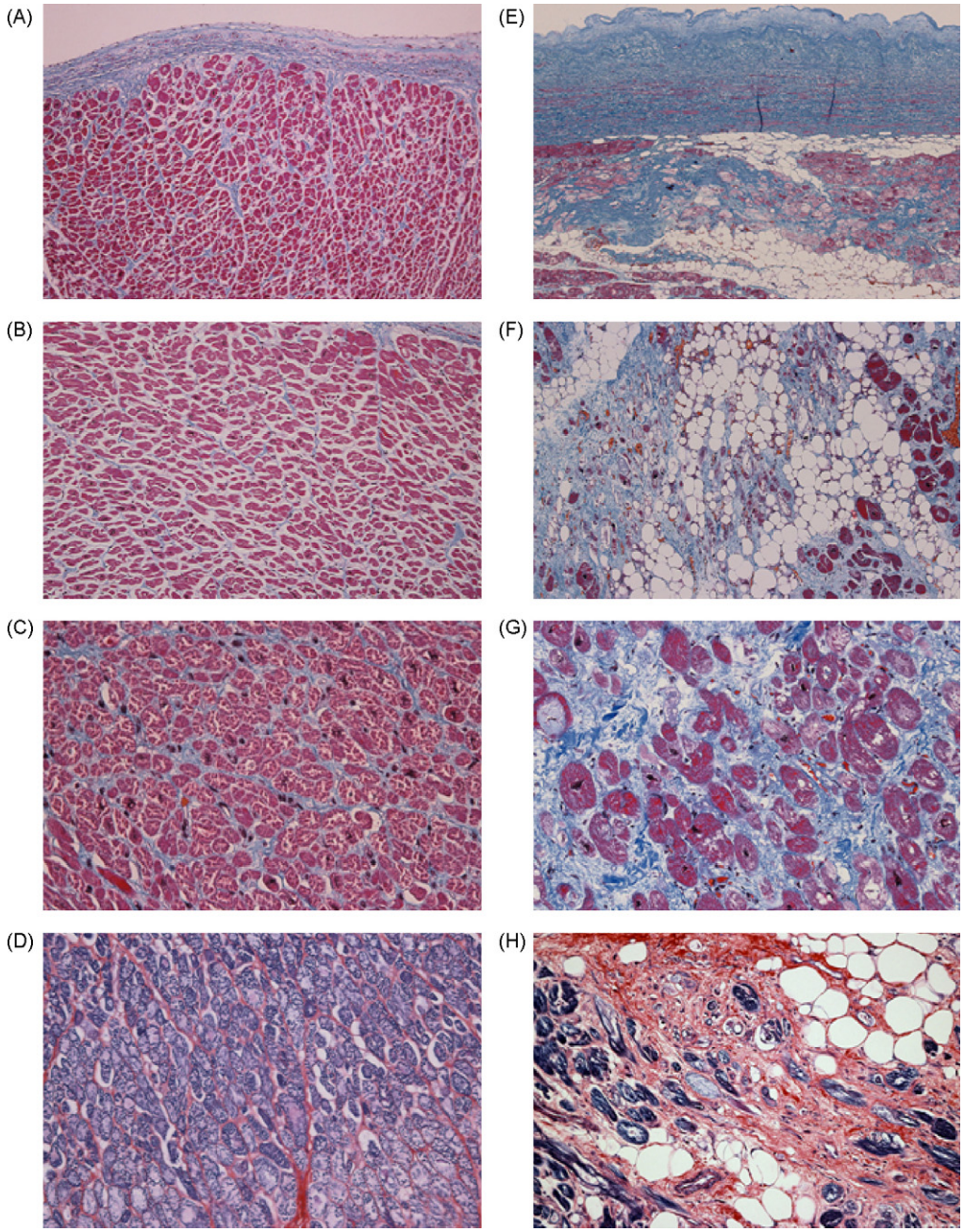

Figure 2 Histopathological features. Left panels (A, B, C, and D) from cases with success of sinus conversion and smaller left atrial volume index (LAVI). Right panels (E, F, G, and H) from case with failure of sinus conversion and greater LAVI. Masson's trichrome stain, original magnification: 10× (A and E), 25× (B and F), 50× (C and G). Phosphotungstic acid-hematoxylin stain, original magnification: 50× (D and H).

Mechanistic relationship between AF and histopathology

Myocardial degeneration and the presence of intracellular fibrosis around cardiomyocytes may interfere with normal electrical conduction and mechanical hemodynamic function and predispose to AF [30,31]. Fibrosis and cardiomyocyte degeneration accounts for electrical heterogeneity, which is directly related to the occurrence of atrial arrhythmia. Incisions created during the maze procedure can block reentrant circuits and promote maintenance of sinus rhythm.

Mitral valve surgery for stenosis or regurgitation can relieve LA pressure and volume overload via reduction of LA size and LA function, thereby promoting maintenance of normal sinus rhythm. LA remodeling is reversible in the early stage of LA structural and functional disturbances [32,33], and previous studies have shown that LA size and function can improve after restoration of sinus rhythm from AF and after repair of mitral valve disease [34,35].

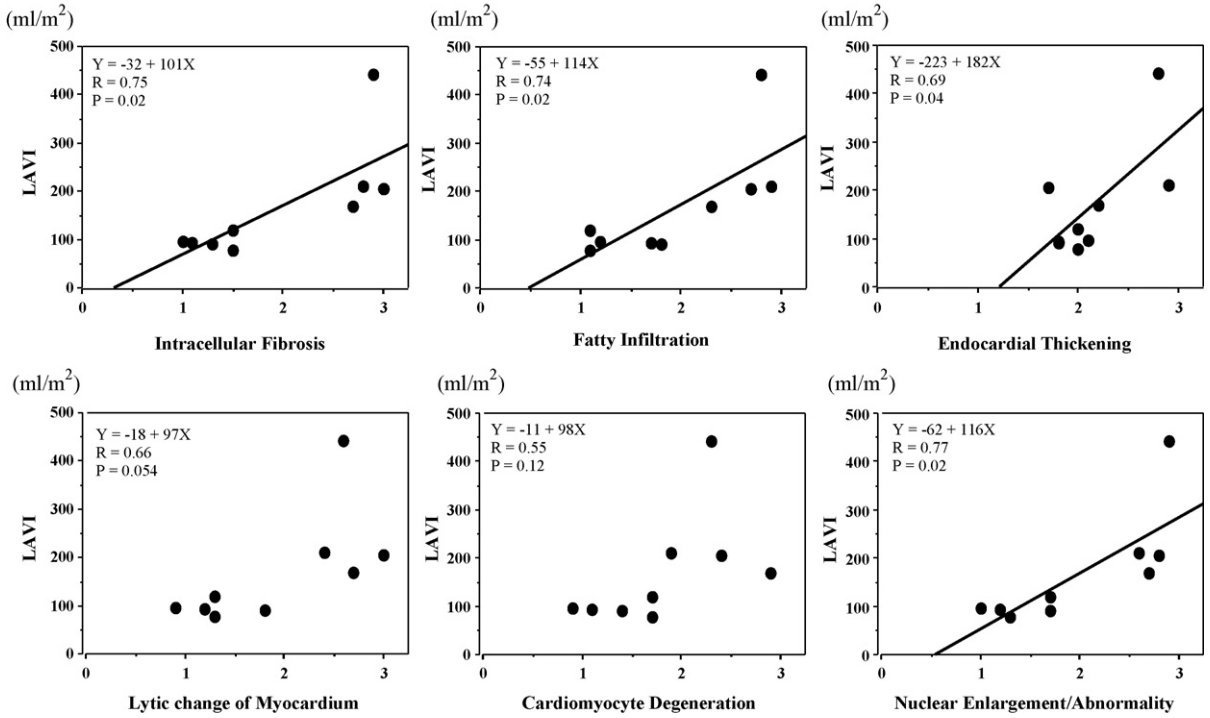

Figure 3 Correlation between left atrial volume index (LAVI) and histopathologic findings. Intercellular fibrosis (left-upper panel); fatty infiltration (middle upper panel); endocardial thickening (right-upper panel); lytic change of myocardium (left-lower panel); cardiomyocyte degeneration (middle-lower panel); nuclear enlargement/abnormalities (right-lower panel).

However, in more advanced stages of remodeling, the larger LA size, extensive intracellular fibrosis, and myocardial degeneration interferes with restoration of sinus rhythm despite correction of valvular malfunction.

Comparison to previous reports

A previous study reported that advanced age, greater CTR, longer-standing AF, lower amplitude f-wave, and greater LA diameter were significant risk factors for failure to achieve and maintain normal sinus rhythm following maze procedures [4—7,9,10,17]. Indeed, the success rate for conversion to sinus rhythm was low in the present study, possibly because the study population was relatively old, with a long duration of AF when compared with study populations from previous reports.

Table 4 Differences in LAVI and histopathological scores in the 2 groups.

Case	Intracellular fibrosis	Fatty infiltration	Endocardial thickening	Autolysis of myocardium	Cardiomyocyte degeneration	Nuclear enlargement/abnormality
Group 1, Successful achievement and maintenance of sinus rhythm						
1	1.1	1.7	1.8	1.2	1.1	1.2
2	1.0	1.2	2.1	0.9	0.9	1.0
3	1.3	1.8	1.8	1.8	1.4	1.7
4	1.5	1.1	2.0	1.3	1.7	1.3
Mean value	1.2 ± 0.2	1.5 ± 0.4	1.9 ± 0.2	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.3
Group 2, Failed achievement or maintenance of sinus rhythm						
5	2.7	2.3	2.2	2.7	2.9	2.7
6	2.8	2.9	2.9	2.4	1.9	2.6
7	2.9	2.8	2.8	2.6	2.3	2.9
8	1.5	1.1	2.0	1.3	1.7	1.7
9	3.0	2.7	1.7	3.0	2.4	2.8
Mean value	2.6 ± 0.6	2.4 ± 0.7	2.3 ± 0.5	2.4 ± 0.7	2.2 ± 0.5	2.4 ± 0.7
p-Value	0.003	0.057	0.163	0.025	0.022	0.023

LAVI, left atrial volume index.
p-Value vs. cases with successful achievement and maintenance of sinus rhythm.

Clinical implications

Surgical procedures to correct AF can be associated with various complications, including sinus arrest and the need for pacemaker implantation [36,37]. Indeed, in the present series, 3 patients who failed to maintain sinus conversion required permanent pacemaker implantation postoperatively. The cut-off value of LAVI determined in the present study may help identify patients with persistent AF who would benefit from surgical intervention while simultaneously avoiding the risk of complications by excluding those who would not likely benefit from surgical intervention.

Certain medications, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone receptor antagonists, can slow the progression of fibrosis [38—40]. In combination with findings from the present study, these observations suggest that the preoperative use of the medications may promote changes in LA size and function that are more favorable in terms of achieving and maintaining sinus rhythm.

Study limitations

This study has several limitations. First, this was neither a prospective study nor a case-controlled study, meaning that patient demographics and concomitant surgical procedure were not matched. Second, patients were only studied through 4 weeks of follow-up. Thus, the mid-term to long-term results remains unknown. Finally, histopathological assessment was performed only in a limited number of patients (who provided informed consent) from the larger cohort of patients, and the resulting statistical power may have been insufficient to demonstrate differences in some parameters. Therefore, a slight discrepancy existed between the results in the correlation between LAVI and LAA histopathology and those in the comparison of LAA histopathology between the 2 groups.

Conclusion

In conclusion, preoperative LAVI was associated with the degree of histopathological changes of the LAA and also predicts failure of sinus conversion after surgery for valvular AF with a cut-off value of 135 ml/m^2.

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